

Do Antidepressants Really Work?

By William Z. Potter, M.D., Ph.D., Foundation of the National Institutes of Health
and Steven M. Paul, M.D., Weill Cornell Medical College

Three recent books and a series of commentaries and reviews in the press raise the question whether widely used antidepressants are really effective in most of the individuals who take them. In an especially high-profile article, Marcia Angell, former editor in chief of *The New England Journal of Medicine* provided a stinging rebuke of psychiatric drugs in general and of course the drug companies that manufacture them. Writing in *The New York Review of Books* Angell seemed to seriously consider the possibility that “psychoactive drugs are useless”. There were also highly visible pieces in *USA Today* and *Newsweek*, the first on a study done by the psychologist Robert DeRubeis headlined “Antidepressant lift may be all in your head,” and the other a cover article on a retrospective “meta-analysis” by the psychologist Irving Kirsch and colleagues of clinical trial data provided to the FDA by pharmaceutical companies and interpreted as evidence that antidepressants were no more effective than [placebo](#) in most patients.



Dr. William Z. Potter



Dr. Steven M. Paul

Mainstream scientists, however, have and continue to understand the same data as showing that antidepressants work well for at least 20 percent of patients on an initial trial. The scientific dilemma is to separate patients who really need a drug from those who will respond to placebo. In the future this should be possible as the field develops better laboratory tests for measuring relevant brain function. In the meantime, the challenge for doctor and patient is the same as for the scientist – to make as good a decision as possible about whether or not to use an antidepressant in each situation without a laboratory test for guidance.

Simply stated, clinical trial data on antidepressants, similar to that for many other classes of drugs, including most cancer and anti-inflammatory drugs, have never shown that more than 60 to 70 percent of patients in any given study improve. And, in many studies, improvement on a placebo (so-called sugar pill with no active drug)

is observed in 30 to 50 percent of patients during the average six week trial period. This could be taken to mean that only about 20 percent of depressed patients truly benefit from their antidepressant medication (i.e. beyond those patients who would benefit from just a placebo), with 30 to 40 percent of patients failing to improve on either drug or placebo.

Why, then are drugs with such limitations widely used as antidepressants by the medical profession? To start with, the [diagnosis of depression](#) based on various reported emotional and physical complaints does not often point to a specific cause, as for example might be revealed by a throat culture for strep throat or an X-ray of a hairline fracture causing pain. Some depressions are caused by specific physical or organic disease (e.g. hypothyroidism) but most have no (as yet) known physical etiology. Given the indisputable complexity of the brain and the myriad biochemical processes involved in normal brain function, any one of which if dysfunctional could contribute to the clinical syndrome we call depression, it would be unrealistic to expect that a single and relatively simple pharmacological intervention would work for all or even most patients. The same is true for many common non-psychiatric disorders, especially cancers, which are due to a vast array of acquired and inherited genetic mutations and environmental insults. Most cancer drugs, for example, are only partially effective in treating a small subgroup of patients with any given tumor type, and unfortunately not for very long. Moreover, we have no blood or brain imaging tests that can reliably diagnose depression or ascertain its severity.

Antidepressant drugs that work only for some patients were [discovered serendipitously](#) in the 1950's; they were being tested for other purposes and used inadvertently in depressed patients who subsequently reported feeling “better”. It was only later that the reported improvement in mood following treatment with these drugs was

coupled to a formal diagnosis of depression and the drugs subsequently tested in controlled clinical trials.

The most widely prescribed class of antidepressants (so-called SSRIs) that has attracted so much recent attention has a specific biochemical action in the brain. SSRIs selectively inhibit the uptake of the neurotransmitter, serotonin, at the neuronal synapse, effectively enhancing the activity of serotonin at only those synapses and in key brain regions. Modern SSRIs evolved from basic brain research to understand how the earlier, serendipitously discovered class of drugs (called tricyclic antidepressants) worked and to synthesize compounds that were free of the tricyclics' toxic side effects (the most serious of which is death with even moderate overdoses).

Given the relative safety of SSRIs it is now common for someone with the symptoms of depression to be prescribed one by their physician, generally a primary care doctor, even though the clinical trial data tell us that only about 1 in 5 such patients will respond better to the drug than placebo over the ensuing four to six weeks. The doctor, however, has no way of selecting only those patients who will benefit from these SSRIs and, therefore, given the extremely low risk of serious side effects, prescribes the drug and follows the patient to see if he or she is among the 60 to 70 percent who will improve. It is almost impossible however to know in such a real-life setting how many patients would have responded to just placebo.

In some forms of depression an individual is so severely impaired that he or she requires hospitalization. Studies done decades ago in hospitalized depressed patients receiving tricyclic antidepressants showed a 60 to 70 percent improvement or response rate but a much lower (20 to 30 percent) improvement rate on placebo, suggesting that for every three such patients treated two are true drug responders. Today, however, such patients are no longer enrolled in placebo controlled clinical trials unless they fall into the 30 to 40 percent who fail to respond to a standard treatment. If a new agent held the promise of a special property such as very rapid response, a short placebo controlled trial could be justified.

Instead, the vast majority of studies are done in outpatients with depression, a clinically diverse group who complain of some symptoms of depression but

also include individuals who are able to carry out most everyday activities of daily living, including work. It is in this patient population that high placebo response rates are often observed. Furthermore, to qualify for an outpatient trial of a new antidepressant, a person need have only five out of ten possible symptoms of depression and thus individuals are enrolled in these studies who have virtually no symptoms in common. Given such mixed groups of patients, it is not surprising that both drug and placebo response rates are highly variable.

Interestingly, some of the articles questioning the general effectiveness of antidepressants over placebo interpret the data as indicating that their real use should be for more serious depression. But the very nature of outpatient clinical trials excludes the most seriously affected individuals who might require hospitalization or pose an acute suicide risk. The measure of "severity" in clinical trials is based on highly subjective responses to questions about feelings, appetite, sleep patterns, etc. At the extremes, individuals who tend to complain about their symptoms can score much higher on such scales than much more impaired stoic, non-complaining persons who deny their real suicidal thoughts. We know that subjective reports about sleep are often very different from the objective laboratory documentation of sleep with EEG. In the not-too-distant future using the tools of functional brain imaging we should be able to objectively document and quantify the abnormal brain "physiology" that underlies depression. We will then have objective and standardized measures of "depression", understood as degree of altered brain function, which are not dependent on subjective or cultural factors influencing how depressed patients rate themselves or are rated by others.

The subjectivity of ratings produces problems in the [interpretation of the data from trials](#). For example, pressures from both patients and investigators to meet entry criteria for trials leads to inflated scores and entry of individuals who would not be expected to need or benefit from a drug. Conversely, patients who tend to minimize symptoms can have a relatively low score but actually be in greater need of the drug than others with higher scores. We know such patients exist because when all patients who improve on drug are subsequently randomized to continue on active drug or be switched to placebo, we observe a 25 to 35 percent difference in relapse rates between the conditions even

among patients without an initially high score. This shows that across the range of entry scores, there are individuals who really do need the medication. Such benefit only becomes clear when one winnows out those who initially improve on placebo which, as noted earlier, can be as high as 50 percent. In fact, the ability of antidepressants to prevent the relapse of depression over many months provides clearer support for their effectiveness than do shorter-term studies of acutely ill patients. The consistent finding of a higher relapse rate into depression of patients switched to placebo who initially improve on an antidepressant also supports the current practice of placing patients with an uncertain degree of depression on medication, since it especially benefits those who require medication not only to improve but also to stay well.

Thus, antidepressants do work better than sugar pills in difficult to define subgroups of depressed individuals and therefore their overall effectiveness (vs. placebo) in large clinical trials conducted in diverse populations is very modest at best. Scientists, physicians and patients cannot be satisfied with this state of affairs. For decades we have been seeking ways of selecting the right patients for a particular antidepressant medication so as to ideally prescribe one only to someone who will really benefit from it.

Studies to better identify individuals [who respond well to specific medications](#) are underway in depression and other disorders using the tools of modern genetics and brain imaging. For instance, genetics already provides a means of identifying people in whom the liver breaks down drugs in such a way that the average dose would be ineffective or toxic. There are promising hints that genetic subtypes may help identify individuals who are more likely to respond to placebo. Most neuroscientists have even greater hope that sophisticated measures of brain function both with surface electrophysiological measures (related to the traditional EEGs used for years in neurology) and more complex functional MRI (same instruments used to look at structures deep inside the brain or other body organ systems) will be able to predict both drug and placebo responders. Emerging data indicates that such measures, when coupled with those from genetics, should allow for likely drug and placebo responders to be reliably identified. Identifying who will respond best to which drug should also be possible with the same laboratory tests but will have its greatest value when we find effective medications for

the 30 to 40 percent of depressed patients who fail to respond to either drug or placebo.

In reality the current generation of antidepressants, including the SSRIs, are arguably really no more effective than the oldest generation of antidepressants discovered by serendipity over a half century ago. As we underscore, despite their usefulness for many depressed patients, there should be little debate about their limitations. Currently used antidepressants do not work particularly well for the majority of patients (as complete remission rates are still relatively low) and they can take weeks to be fully effective. Antidepressants do work however for many patients and like many cancer drugs they can literally save lives. Still it is also true that the considerable advances in neuroscience and our understanding of both normal and abnormal brain function over the past 20 to 30 years have yet to fully translate into more effective approaches to treating depression. We believe given the recent research advances in genetics and imaging however that this rather depressing state of affairs is about to change and that more effective and even rapidly-acting antidepressant drugs as well as non-pharmacological interventions may well be on the horizon. We look forward to that future of more effective treatments and the means of matching the best treatment, including some placebo equivalent, to anyone with depression.

FURTHER READING

1. [“Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration.”](#) Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. *PLoS Med.* 2008 Feb;5(2):e45.
2. [“History of the Use of Antidepressants in Primary Care.”](#) Joseph A. Lieberman III, M.D., (*Primary Care Companion J Clin Psychiatry* 2003;5[*suppl 7*]:6–10)
3. [“Rating Scales in Depression: Limitations and Pitfalls.”](#) Per Bech, M.D. ; *Dialogues Clin Neurosci.* 2006 June; 8(2): 207–215.
4. [Translating scientific opportunity into public health impact: a strategic plan for research on mental illness.](#) Insel TR *Arch Gen Psychiatry.* 2009 Feb; 66(2):128-33.